Title: Lung cancer CT screening – are we ready to consider screening biennially in a subgroup of low risk individuals?

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Most published research on low-dose CT screening for lung cancer pertains to annual screening (1). In this issue, Schreuder and colleagues explore the possibilities for extending the inter-screening interval on an individual basis (2) . Using data from the US National Lung Screening Trial (3), they build up a logistic regression model of risk of a lung cancer at the second annual screen or in the year following it, based on subject characteristics and radiological observations including nodule attributes at the first screen. The logistic model incorporates polynomial regression coefficients where appropriate. They compare their model with other possible prediction models for this specific endpoint and find it to be superior.

The authors conclude that there is scope for extending the interval for some screenees. From their model, they project that for different risk thresholds, at the second screen, 2558 (10.4%), 7544 (30.7%), 10,947 (44.6%), 16,710 (68.1%), and 20,023 (81.6%) of the 24,368 screens could have been omitted, at the cost of delayed diagnosis of 0 (0.0%), 8 (4.6%), 17 (9.8%), 44 (25.3%), and 70 (40.2%) of the 174 lung cancers, respectively.

These observations need to be validated prospectively and evaluated in terms of cost-effectiveness, but they are certainly interesting and potentially very important. Another question which remains is, for the cancers whose diagnosis would be delayed as a result of postponing the second screen to two years after the first, what is lost in terms of stage of disease at diagnosis and the consequent effect on mortality?

The authors report the (actual, observed) stage at diagnosis of the cancers which would be missed for the various thresholds. Apart from the lowest risk threshold, for which 10% of screens could be avoided with an estimated zero loss in terms of later diagnosis, for any given threshold, the majority of tumours which would have had their diagnosis delayed were diagnosed at stage I or II. Thus, the delay might well mean a substantial proportion having a good prognosis replaced by a poor one. This will be an important ingredient in a cost-

effectiveness analysis. A future modelling exercise might target the issue of screening those whose tumours are most likely to benefit from early diagnosis, while not screening those destined either not to develop the disease or to be diagnosed at late stage despite our best efforts at early detection.

We reiterate that the results here will need validation. However, they are important and will stimulate further work to improve the process of early detection of lung cancer for both provider and public.

In the European position statement on lung cancer screening (EUPS) (4), the management of prevalent lung nodules is discussed in detail and it was argued that nodule management will largely depend on size criteria, however, volumetry is now considered essential, but diameter cut-offs will also need to be provided for cases where segmentation is not possible.

The Nelson trial group have analysed volume, volume doubling time, and volumetry-based diameter of 9681 non-calcified nodules detected by CT screening in 7155 participants and provided a very compelling argument to consider screening a sub-group of individuals on a biennial basis.

They found that the Lung cancer probability was not significantly different between the participants who had nodules < 100 mm^3 in volume and those participants who had no detected nodules (0·6% [95% CI 0·4–0·8] vs 0·4% [0·3–0·6]; p=0·17). The participants who had nodules between 100–300 mm^3 had a significantly greater probability of developing lung cancer compared to participants with no screening-detected nodules (2·4% [95% CI 1·7–3·5]; p<0.0001 and were consider ‘indeterminate’ and requiring 3 or 12 months follow up CT scan, whist nodules of 300mm^3 or greater had a significantly greater chance of developing lung cancer.

However, in about half of the NELSON participants, no pulmonary nodules were detected and their 2-year probability of developing a lung cancer was 0·4%. Thus it may be argued that they could have a screening interval of at least 2 years (5).

There have been two major publications based on modelling screening intervals from the UKLS (6, 7) and the and the International Early Lung Cancer Action Program (7). Whilst Duffy et al estimated that two-yearly screening could potentially be more cost effective, Yankelevitz et al. argued that we should focus on how the interval between screens affects the stage distribution prior to thinking about changing from annual screening intervals.

Patz et al examined the NLST participants who had a negative prevalence screen and found that they had a substantially lower risk of developing lung cancer compared to individuals with a positive prevalence screen (8) thereby providing further support for the argument to consider biennial screening.

The cost effectiveness of lung cancer screening has been analysed utilising microsimulation modelling by ten Haaf et al (9).Their results indicate that we have to seriously consider a range of screening scenarios, and especially the interactions between the smoking eligibility criteria as well as the screening interval, both of which influence the cost-effectiveness of each scenario.

The EUPS argued that future decisions on interval timing should be based on risk, psychosocial effects, cost-effectiveness, and the feasibility of implementation, all of which require further investigation. While we would argue that this remains the case, the results of Schreuder et al give valuable food for thought.

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